over Waterhouse et al. and Wasseneger et al., taken with Dougherty et al.

Applicants do wish to note for completeness that Applicants have **never argued** that "Dougherty et al, as relied on by the Examiner, discloses that 21 nt SRMs are detected in *C. elegans*" (action page 20). It would seem that the Examiner has misinterpreted Applicant's last response dated 4 June 2002, page 6 lines 6-8. Although Applicants did note in the previous response that Dougherty et al. was concerned with *C. elegans* and not plants, the primary argument was not based on the difference between plants and nematodes. In fact, the present inventors were the first to demonstrate the actual existence and detectability of silencing-associated SRMs in **any** organism.

The Examiner has set forth numerous new grounds of rejection.

First, the Examiner has rejected the claim for priority due to a typographical error in the originally filed declaration, and because of a typographical error in the first line of the specification.

Next, claims 1, 5-17, 21, and 32-34 are rejected under 35 U.S.C. §112 first paragraph, as lacking enablement commensurate in scope with the claims.

Next, the Examiner has rejected claims 26-29 under 35 U.S.C. §112 first paragraph for lacking adequate written description.

Next, the Examiner has rejected claims 11-17 under 35 U.S.C. §112 second paragraph as allegedly indefinite for failing to specifically point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner has rejected claims 12-14 under 35 U.S.C. §102(b) as allegedly anticipated by Cleuziat et al., US Patent 5,849,547. The Examiner further rejects claim 12 under 35 U.S.C. §102(b) as allegedly anticipated by Mueller et al., The Plant Journal, 7(6): 1001-1013, 1995.

The Examiner has rejected claims 12-15 under 35 U.S.C. §103(a) as allegedly unpatentable over Cleuziat et al., US Patent 5,849,547.

In a concluding statement the Examiner notes that claims 1, 5-11, 16-17, 21, 26-29, and 32-34 are free of the prior art, but are subject to other rejections.

The foregoing constitutes the entirety of the objections and rejections raised in the August 28, 2002 Official Action. In light of the present claim amendments and the following remarks, each of the above-noted rejections under 35 U.S.C. § 112, first and second paragraphs, 35 U.S.C. § 102 and § 103 is respectfully traversed.

FORMAL REQUIREMENTS FOR RIGHT OF PRIORITY HAVE BEEN MET

The Examiner has rejected the claim for priority due to a typographical error in the originally filed declaration, and because of a typographical error in the first line of the specification.

Applicants have amended the priority claim in the specification in accordance with the Examiner's requirements. With regard to the Examiner's requirement for a new declaration, Applicants respectfully submit that this should not be necessary to meet the formal requirements of a priority claim. In MPEP §201.14, the formal requirements for priority are discussed. Here it states that "Unless provided in an application data sheet, 37 CFR 1.63 requires that the oath or declaration must identify the foreign application for patent or inventor's certificate for which priority is claimed under 37 CFR 1.55, and any foreign applications having a filing date before that of the application on which priority is claimed, by **specifying the application number, country, day, month, and year of its filing**." *(Emphasis added)*

The priority claim in the originally submitted declaration meets all of these requirements. Accordingly, Applicants respectfully request that the Examiner accept the

originally filed declaration, in spite of the minor typographical error.

CLAIMS 1, 5-17, 21, and 32-34 AS AMENDED ARE FULLY ENABLED BY THE DISCLOSURE IN THE SPECIFICATION

The Examiner has maintained the rejection of claims 1, 5-17, 21, and 32-34 under 35 U.S.C. §112 first paragraph for allegedly failing to be commensurate in scope with the disclosure in the specification. Applicants respectfully traverse.

At the outset, Applicants note that the standards for enablement require that the disclosure must describe the invention such that one of ordinary skill in the art could make and use the invention without undue experimentation.

MPEP at § 2164 states that,

> The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention.

In § 2164.01, the MPEP continues,

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

(*Quoting United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The test for enablement is the balancing of several specifically prescribed factors listed in MPEP § 2164.01(a), as follows:

> These factors include, but are not limited to:
> (A) The breadth of the claims;
> (B) The nature of the invention;

(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. (*Citation omitted.*)

Further,

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

(MPEP § 2164.01, *emphasis supplied, citations omitted.*)

Thus an enabled invention may require some degree of experimentation, provided that the level of experimentation is not undue. It is respectfully submitted that in the instant case, the experimentation required is merely routine and further, extensive guidance for such experimentation is provided in the specification.

First, in response to the Examiner's general assertions of inadequate enablement, although not agreeing with the Examiner's comments, Applicants believe that the claims now correspond to that subject matter acknowledged as enabled by the Examiner, other than in two respects:

(i) The claims are not limited to instances in which the silencing of the target gene is correlative to a phenotype exhibited by a plant; and

(ii) The claims are not limited to instances in which the target gene is a transgene or endogenous gene that is the same as a transgene.

Applicants respectfully submit that these changes would be unduly limiting, because either of these characteristics in the claim could actually be interpreted as excluding the embodiments of the invention shown in Example 1, page 25, lines 21 onwards. In that example a viral PVX-GFP replicon is introduced into a wild-type plant via agro-infiltration. The viral infection was monitored and it was shown that PVX SRMs were present in leaves of the plant, demonstrating that the viral-silencing by the plant, underlying the natural RNA-mediated defence, is detectable by SRMs. Even if viral silencing was considered to be a phenotype, the PVX genome may not be seen as a transgene or endogenous gene that is the same as a transgene. Indeed this is reflected in the official action page 5, line 4. See also claims 9 and 10.

In terms of the requirement of exogenous nucleic acid - this is one key way to **initiate** silencing. Numerous methods of initiating silencing are found in the prior art, and this is why that part of the method is in the preamble of the claim.

The exogenous nucleic acid is not an essential feature of the presently claimed invention - which is a **detection** method, as recited in the steps of the claim. Accordingly, Applicants respectfully submit that the claims should not be limited to exogenous nucleic acids.

In addition to a general discussion of the alleged inadequacy of the enablement provided in the present specification, the Examiner has raised issues with regard to specific sets of claims. These arguments are addressed below.

First, with regard to claims 1, 5-7, 21, and 32-34, the Examiner states that the claims should be limited to SRMs which share homology with specific target gene sequences. The Examiner also states that there does not appear to be a correlation between the presence of SRMs and gene silencing.

Applicants submit that it is clear from the claims as originally recited that there is some degree of homology between the SRMs and the target gene. For example, in order for SRMs to bind to their target gene, the skilled artisan would recognize that they must share some degree of homology. This is further supported in the specification, for example at page 5, lines 2-5; page 9, lines 16-20; and page 14, lines 10-15, all of which discuss homology of the SRM with the target gene.

Nonetheless, solely in the interest of expediting prosecution, and without agreeing with the Examiner's grounds of rejection, Applicants have amended the claims to recite a step of determining the degree of sequence identity or similarity between the SRMs and the target gene.

Next, Applicants submit that contrary to the Examiner's assertions, there is a clear correlation between SRM expression and gene silencing. The Examiner takes the position that "in the absence of a phenotype it is unpredictable if a target gene is silenced" (action, page 8, lines 2-4). Applicants respectfully disagree, and submit that even for endogenous genes or transgenes (for example), gene silencing can be detected without correlation to a phenotype.

The present invention provides precisely a method for detecting whether a target gene is silenced, regardless of whether the target gene corresponds to a phenotype. As stated in the discussion on page 26, lines 14-24, the SRMs were **consistently** found in contexts where PTGS was occurring and were **never** found where it wasn't.

In principle, one can envisage instances where gene-silencing, even of endogenous genes or transgenes, does not give rise to a change in phenotype e.g. where other genes may complement the loss of effect. Nevertheless, in essence, the Examiner appears to be asserting that SRMs-based methods can only be relied on if there is confirmation from a phenotype. There is absolutely no evidence for this position, whether in

the specification, or in the art published before or since. The fact is that all the evidence points towards SRMs detection alone being a definitive and sufficient indicator of silencing. Indeed, it has particular utility where phenotype cannot be readily or easily monitored.

It would be unduly limiting to Applicant to require introduction of a specific phenotype feature. Such a claim could be readily avoidable by a competitor for the reasons set forth above.

Second, the Examiner discusses claims 8-10. Here the Examiner again submits that absent a phenotypic change, gene silencing cannot be determined by measuring SRMs.

Applicants again submit, as above, that a phenotypic correlation is not required to detect gene silencing, in light of the clear and consistent correlation between SRMs and PTGS which is described throughout the specification.

Third, the Examiner discusses claim 11. Here the Examiner again asserts that the specification is only enabling for detection of SRMs in relation to exogenous genes. Further, the Examiner asserts that the specification is only enabling for gene silencing detection in plants.

With regard to detection of genes other than exogenous genes, Applicants again submit that the instant methods are clearly enabled for detection of endogenous as well as exogenous genes, as described and exemplified above, and in the specification.

With regard to the Examiner's contention that the claims should be limited to plants, Applicants submit that this unduly limits Applicant's invention. The claimed methods would function in any organism which exhibits PTGS, including plants and animals. This is evidenced as set forth above, by the showing at page 26, lines 14-24, in which whenever there is PTGS, SRMs are detected. Accordingly, it is reasonable to conclude that regardless of the type of organism (i.e. plants or animals), as long as there is PTGS, SRMs will be

detectable. This conclusion is further supported by the experiment set forth as Example 2, in which SRMs were detected in *C. elegans* (a non-plant organism.) Accordingly, Applicants submit that the claims need not be limited to plants.

Nonetheless, solely in the interest of expediting prosecution, and without agreeing with the Examiner's grounds of rejection, Applicants have amended claim 11 to recite "plant."

Fourth, the Examiner addresses claims 12-16. Here the Examiner reiterates that SRMs do not necessarily correspond to gene silencing, and that the claims encompass any organism, and are not limited to plants.

In response, Applicants again submit that SRMs do correspond to gene silencing for the reasons set forth above, and that the specification fully enables claims to the method in any organism.

Nonetheless, without agreeing with the Examiner's grounds of rejection, and solely for the purpose of expediting prosecution, Applicants note that claim 12 has been amended to recite "plant", and that claim 16 has been canceled.

Lastly, the Examiner discusses claim 17. Here the Examiner once again asserts that the claims should be limited to plants in light of the restriction requirement and further in light of the teachings in the prior art.

In response, Applicants again submit as set forth above that these aspects of the invention are enabled by the disclosure as originally filed. Nonetheless, solely in the interest of expediting prosecution, and without agreeing with the Examiner's grounds of rejection, Applicants have amended claim 17 to recite "plant."

In summary, Applicants submit that the full scope of the claims as presently recited is enabled by the specification such that it can be practiced without undue experimentation, and accordingly, withdrawal of the rejection is respectfully requested.

ALL CLAIMS ARE FULLY DESCRIBED BY THE DISCLOSURE IN THE SPECIFICATION

Claims 26-29 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the written description requirement. It is the Examiner's position that the specification does not adequately disclose DNA sequences that encode all short RNA molecules, or antisense RNA molecules within the scope of the invention.

Applicants respectfully traverse this rejection. As noted in the MPEP at § 2163,

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Furthermore, the written description guidelines set forth in the Federal Register Vol. 66, No. 4, January 5, 2001 state that "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics, so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention."(page 1105, column 3). "An applicant may also show that an invention is complete by disclosure of sufficiently detailed , relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e.: complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." (Page 1106, column 1).

In the instant case, specific molecules (RNA molecules of a specific size) are described in terms of structure (size and similarity to a target gene), and in terms of function (are expressed in PTGS organisms and produce gene silencing.) Accordingly, Applicants respectfully submit that these claims

as originally recited are fully described.

Nonetheless, in the interest of expediting prosecution, and without agreeing with the Examiner's rejection, Applicants have canceled claims 26-29.

CLAIMS 11, 12 and 17 AS AMENDED FULLY COMPLY WITH THE DEFINITENESS REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH

In rejecting claim 11, the Examiner states that the terms "said organism" and "the organism" in steps (vii) and (viii) lack antecedent basis. Applicants have amended claim 11, so as to provide antecedent basis throughout the claim.

The Examiner further states that claim 12 is incomplete because the steps of the method do not explicitly refer back to the preamble of the claim, noting that if the format of claim 17 is adopted, then this grounds of rejection will be withdrawn.

Applicants have amended claim 12 in accordance with the Examiner's helpful suggestion.

The Examiner also has rejected claim 17 for lacking antecedent basis in the recitation of "said organism" in steps (i) and (ii).

Applicants respectfully direct the Examiner's attention to the fact that the recitation of "said organism" in claim 17 was deleted and replaced with the recitation "said plant" in the amendment filed April 19, 2001. Accordingly, this grounds of rejection should be withdrawn.

CLAIMS 12-14 AS AMENDED ARE NOT ANTICIPATED BY CLEUZIAT ET AL.

The Examiner has rejected claims 12-14 under 35 U.S.C. 102(b) as allegedly anticipated by Cleuziat et al., US Patent 5,849,547.

The Examiner states that the claims as recited essentially read on the process of Northern Blotting. It is the Examiner's position that the statement that the isolated RNA molecules "are associated with target gene silencing" in

the preamble of the claim does not lend patentable weight to the claim.

Applicants respectfully submit that the Examiner cannot summarily ignore the preamble of the claims. See MPEP 2111.02:

> "[A] claim preamble has the import that the claim as a whole suggests for it." Bell Communications Research, Inc. v. Vitalink Communications Corp. , 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995). "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). See also Kropa v. Robie , 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951) (A preamble reciting "An abrasive article" was deemed essential to point out the invention defined by claims to an article comprising abrasive grains and a hardened binder and the process of making it. The court stated "it is only by that phrase that it can be known that the subject matter defined by the claims is comprised as an abrasive article. Every union of substances capable inter alia of use as abrasive grains and a binder is not an 'abrasive article.'" Therefore, the preamble served to further define the structure of the article produced.).
>
> PREAMBLE STATEMENTS LIMITING STRUCTURE
>
> Any terminology in the preamble that limits the structure of the claimed invention must be treated as a claim limitation. See, e.g., Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989).

Further, the Examiner must consider all parts of the claim when evaluating the prior art:

> "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

Applicants respectfully submit that the recitation "are associated with target gene silencing" is necessary to the life and meaning of the claim, in that it indicates the specific type of RNA molecules which are isolated. These RNA molecules must be of a specific size and sequence, and accordingly, this recitation provides structure, and should be considered as a claim limitation by the Examiner.

Nonetheless, in the interest of expediting prosecution, and without agreeing with the Examiner's rejection, Applicants have amended claim 12 in accordance with former claim 16, which was not subject to this rejection, and thus these grounds of rejection are believed overcome.

CLAIMS 12 AS AMENDED IS NOT ANTICIPATED BY MUELLER ET AL.

The Examiner further rejects claim 12 under 35 U.S.C. 102(b) as allegedly anticipated by Mueller et al., The Plant Journal, 7(6): 1001-1013, 1995.

The Examiner again states that the claims as recited essentially read on the process of Northern Blotting, because the preamble of the claim does not lend patentable weight to the claim.

Applicants reiterate that in this case, the preamble of the claim does lend patentable weight, for the reasons set forth above.

Nevertheless, as described above, Applicants have amended claim 12 in accordance with former claim 16, which was not subject to this rejection, and thus these grounds of rejection are believed overcome.

CLAIMS 12-15 AS AMENDED ARE PATENTABLE OVER CLEUZIAT ET AL.

The Examiner has rejected claims 12-15 under 35 U.S.C. 103(a) as being unpatentable over Cleuziat et al., US Patent 5,849,547.

This grounds of rejection is essentially the same as those set forth above. The Examiner again states that the

claims as recited read on the process of Northern Blotting, because the preamble of the claim does not lend patentable weight to the claim. Applicants strenuously disagree with the Examiner's position in this regard for the reasons set forth above.

Nevertheless, as noted above, Applicants have amended claim 12 in accordance with former claim 16, which was not subject to this rejection, and accordingly, these grounds of rejection are believed overcome.

CONCLUSION

In view of the present claim amendments, and the foregoing remarks, it is respectfully urged that the rejections set forth in the August 28, 2002 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

DANN, DORFMAN, HERRELL AND SKILLMAN

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Appendix A

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In the Specification:

Please replace the paragraph at page 1, line 2 with the following paragraph:

The present application claims priority under 35 U.S.C. §119[(e)](a-d) to GB application number 9925459.1, filed October 27, 1999.

In the claims:

Please amend claims 1, 9, 10, 11, 12, and 17 as follows:

1. (Twice amended) A method of [determining the occurrence of target gene silencing] detecting the silencing of a target gene in a plant, which method comprises the steps of:

(i) obtaining a sample of material from said plant,

(ii) producing a nucleic acid extract from said sample,

(iii) analyzing said extract such as to determine the presence or absence of short RNA molecules which are 21-25 nucleotides in length (SRMs) in said [nucleic] extract,

(iv) characterizing any SRMs which are present in said extract such as to determine sequence identity or similarity with said target gene, and

(v) correlating the presence of said SRMs in the extract with the occurrence of [said target] gene silencing in said plant.

9. (Twice amended) A method in accordance with claim [8] 1, wherein the silencing of said target gene [is] in the plant is associated with pathogen derived resistance.

10. (Twice amended) A method in accordance with claim [8] 1,

wherein the silencing of said target gene in the plant is associated with modification of a specific trait by co-suppression of the target gene.

11. (Twice amended) A method of identifying a silenced target gene in a plant in which gene silencing is detected as claimed in claim [8] 1, which method further comprises the steps of:

[(vii)] (vi) preparing a library of genes from said [organism] plant, and

[(viii)] (vii) identifying those genes in said library which share sequence identity or similarity with any SRMs which are present in the extract as being genes which are silenced in the [organism] plant.

12. (Amended) A process for isolating one or more RNA molecules associated with target gene silencing from a sample of material from a plant, wherein the RNA molecules are SRMs which share sequence identity with the target gene, which process comprises the steps of:
(a) producing a nucleic acid extract from said sample,
(b) purifying said extract to produce purified RNA molecules by carrying out at least one purification step selected from the following steps (i) filtration; (ii) differential precipitation (iii) ion exchange chromatography, such as to isolate said SRMs.

17. (Twice amended) A process for isolating a silencing agent comprising SRMs for a target gene from a plant, which process comprises the steps of:

(i) silencing said target gene in said plant,

(ii) obtaining a sample of material from said plant,

(iii) performing a process in accordance with claim [16] 12 to isolate said SRMs.

Please cancel claims 8, 16, and 26-29.